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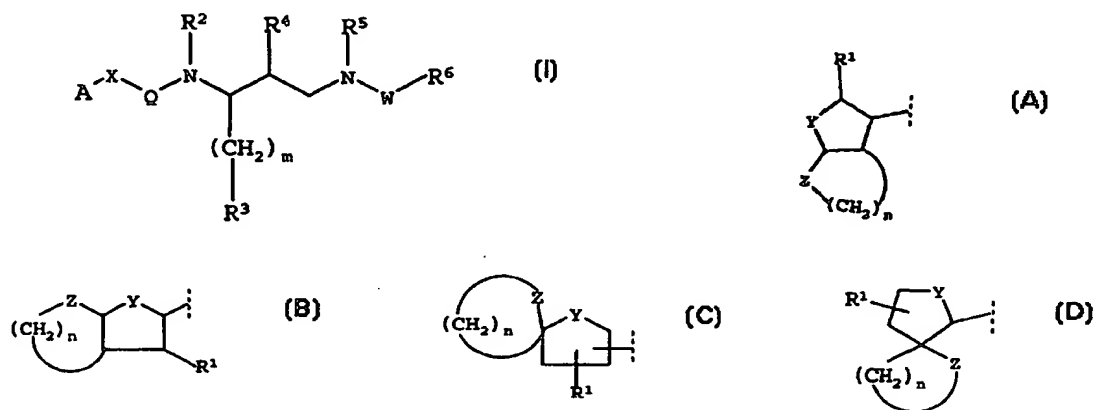
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12Q 1/00	A2	(11) International Publication Number: WO 99/67417 (43) International Publication Date: 29 December 1999 (29.12.99)
(21) International Application Number: PCT/US99/14119 (22) International Filing Date: 23 June 1999 (23.06.99) (30) Priority Data: 60/090,393 23 June 1998 (23.06.98) US (71) Applicant (for all designated States except US): THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; National Institutes of Health, Office of Technology Transfer, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ERICKSON, John, W. [US/US]; 5406 Jefferson Boulevard, Frederick, MD 21703 (US). GULNIK, Sergei, V. [US/US]; 8004 Meadowview Drive, Frederick, MD 21702 (US). (74) Agents: GAGALA, Bruce, M. et al.; Leydig, Voit & Mayer, Ltd., Suite 4900, Two Prudential Plaza, 180 North Stetson, Chicago, IL 60601-6780 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.

(54) Title: FITNESS ASSAY AND ASSOCIATED METHODS



(57) Abstract

The present invention provides an assay for determining the biochemical fitness of a biochemical species in a mutant replicating biological entity relative to its predecessor. The present invention further provides a continuous fluorogenic assay for measuring the anti-HIV protease activity of protease inhibitor. The present invention also provides a method of administering a therapeutic compound that reduces the chances of the emergence of drug resistance in therapy. The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt, a prodrug, a composition, or an ester thereof, wherein A is a group of formulas (A), (B), (C) or (D); R¹, R², R³, R⁵ or R⁶ is H, or an optionally substituted and/or heteroatom-bearing alkyl, alkenyl, alkynyl, or cyclic group; Y and/or Z are CH₂, O, S, SO, SO₂, amino, amides, carbamates, ureas, or thiocarbonyl derivatives thereof, optionally substituted with an alkyl, alkenyl, or alkynyl group; n is from 1 to 5; X is a bond, an optionally substituted methylene or ethylene, an amino, O or S; Q is C(O), C(S), or SO₂; m is from 0 to 6; R⁴ is OH, =O (keto), NH₂, or alkylamino, including esters, amides, and salts thereof; and W is C(O), C(S), S(O), or SO₂. Optionally, R⁵ and R⁶, together with the N-W bond of formula (I), comprise a macrocyclic ring.

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6. The assay of claim 2, wherein said infectious microorganism is a malarial parasite.

7. The assay of claim 6, wherein said malarial
5 parasite is a plasmodium species.

8. The assay of claim 2, wherein said infectious microorganism is a bacterium.

10 9. The assay of claim 1, wherein said predecessor is a cancer cell.

10. The assay of claim 9, wherein said cancer replicating biological entity is a rapidly growing tumor
15 cell.

11. The assay of any one of claims 1-10, wherein said biochemical target of said predecessor is an enzyme and said compound inhibits said enzyme of said
20 predecessor.

12. The assay of any one of claims 3-5, wherein said biochemical target of said predecessor is a viral protease, a viral reverse transcriptase, a viral
25 polymerase, a viral enzyme, or a viral protein.

13. The assay of claim 6 or 7, wherein said biochemical target of said malarial parasite is a plasmepsin, a plasmodial enzyme, or a protein.

36. The method of claim 35, wherein $K_{inh-mut}$, $K_{inh-pred}$, $k_{cat-mut}$, $k_{cat-pred}$, K_M-mut , and K_M-pred are each measured.

5 37. The method of claim 35 or 36, wherein K_{inh} is K_i .

38. The method of claim 35 or 36, wherein K_{inh} is K_d .

39. The assay of claim 1, wherein said predecessor
10 is a wild-type HIV strain and said mutant has at least one mutation in the biochemical target thereof.

40. The method of claim 20, wherein said replicating disease-causing replicating biological entity
15 is a wild-type HIV strain and said mutant has at least one mutation in the biochemical target thereof.

41. The assay of claim 1, wherein said predecessor has at least one mutation in the biochemical target
20 thereof, and said mutant has at least two mutations in the biochemical target thereof.

42. The method of claim 20, wherein said replicating disease-causing replicating biological entity
25 has at least one mutation in the biochemical target thereof, and said mutant has at least two mutations in the biochemical target thereof.

43. The method of claim 39 or 40, wherein said
30 mutant has at least one active site mutation.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 493/04, 491/04, 495/04, A61K 31/34, C12Q 1/37, A61K 31/445	A3	(11) International Publication Number: WO 99/67417 (43) International Publication Date: 29 December 1999 (29.12.99)
(21) International Application Number: PCT/US99/14119 (22) International Filing Date: 23 June 1999 (23.06.99) (30) Priority Data: 60/090,393 23 June 1998 (23.06.98) US (71) Applicant (for all designated States except US): THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; National Institutes of Health, Office of Technology Transfer, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ERICKSON, John, W. [US/US]; 5406 Jefferson Boulevard, Frederick, MD 21703 (US). GULNIK, Sergei, V. [US/US]; 8004 Meadowview Drive, Frederick, MD 21702 (US). (74) Agents: GAGALA, Bruce, M. et al.; Leydig, Voit & Mayer, Ltd., Suite 4900, Two Prudential Plaza, 180 North Stetson, Chicago, IL 60601-6780 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 28 September 2000 (28.09.00)
(54) Title: FITNESS ASSAY AND ASSOCIATED METHODS		
(57) Abstract <p>The present invention provides an assay for determining the biochemical fitness of a biochemical species in a mutant replicating biological entity relative to its predecessor. The present invention further provides a continuous fluorogenic assay for measuring the anti-HIV protease activity of protease inhibitor. The present invention also provides a method of administering a therapeutic compound that reduces the chances of the emergence of drug resistance in therapy.</p>		

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/14119

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D493/04 C07D491/04 C07D495/04 A61K31/34 C12Q1/37
A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 766 842 A (HEEFNER DONALD L ET AL.) 16 June 1998 (1998-06-16) column 1, line 12 - line 40; claims 1,20	1,5,12
X	KLABE, RONALD M. ET AL.: "Resistance to HIV Protease Inhibitors: A Comparison of enzyme Inhibition and antiviral Potency" BIOCHEMISTRY, vol. 37, no. 24, 1998, pages 8735-8742, XP002126126 Abstract	1,5,12

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

6 June 2000

Date of mailing of the international search report

13. 6. 00

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NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/14119

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BORMAN, ANDREW M. ET AL: "Resistance of human immunodeficiency virus type 1 to protease inhibitors: selection of resistance mutations in the presence and absence of the drug" J. GEN. VIROL. , vol. 77, no. 3, 1996, pages 419-426, XP002126127 abstract ----	1,5,12
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/14119

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 723 490 A (ROGER D. TUNG) 3 March 1998 (1998-03-03) the whole document ----	47-62
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/14119

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1-45
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 /4119

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-62

1. Claims: 1-46

Assays for determining evolutionary response of a viral protease to a protease inhibitor and methods of administering compounds identified using this assay, and afluorigenic assay for measuring anti-Hiv protease activity of a protease inhibitor.

2. Claims: 47-62

Method of preventing the development of drug resistance in an HIV infected mammal by administering compounds that inhibit development of drug-resistance.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 /4119

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 47-62 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Further defect(s) under Article 17(2)(a):

Claims Nos.: 20-45

Rule 39.1(iv) PCT- Method of treatment of the human or animal body by therapy

Continuation of Box I.2

Claims Nos.: 1-45

The claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Present claims 1-45 relate to a large number of possible assays. In fact, the claims contain so many options, variables, that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely for an assay for determination of the activity of a viral protease of a mutant HIV-1 or HIV-2 in relation to its predecessor comprising obtaining a predecessor, determining the activity of the protease of said predecessor in the presence of a protease inhibitor, determining the activity of said protease inhibitor and comparing the two protease activities. (i.e. the first subject-matter of claim 12 when referring back to claims 1 via claim 5).

The description does not provide a proper support within the meaning of Article 5 and 6 PCT for any other embodiment covered by claims 1-45.

Moreover claims 20-45 refer to therapeutic compounds which are not characterised by any technical feature which would allow the formulation of a search for these claims or which would allow a meaningful comparison with methods of the state of the art.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/14119

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information on patent family members

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